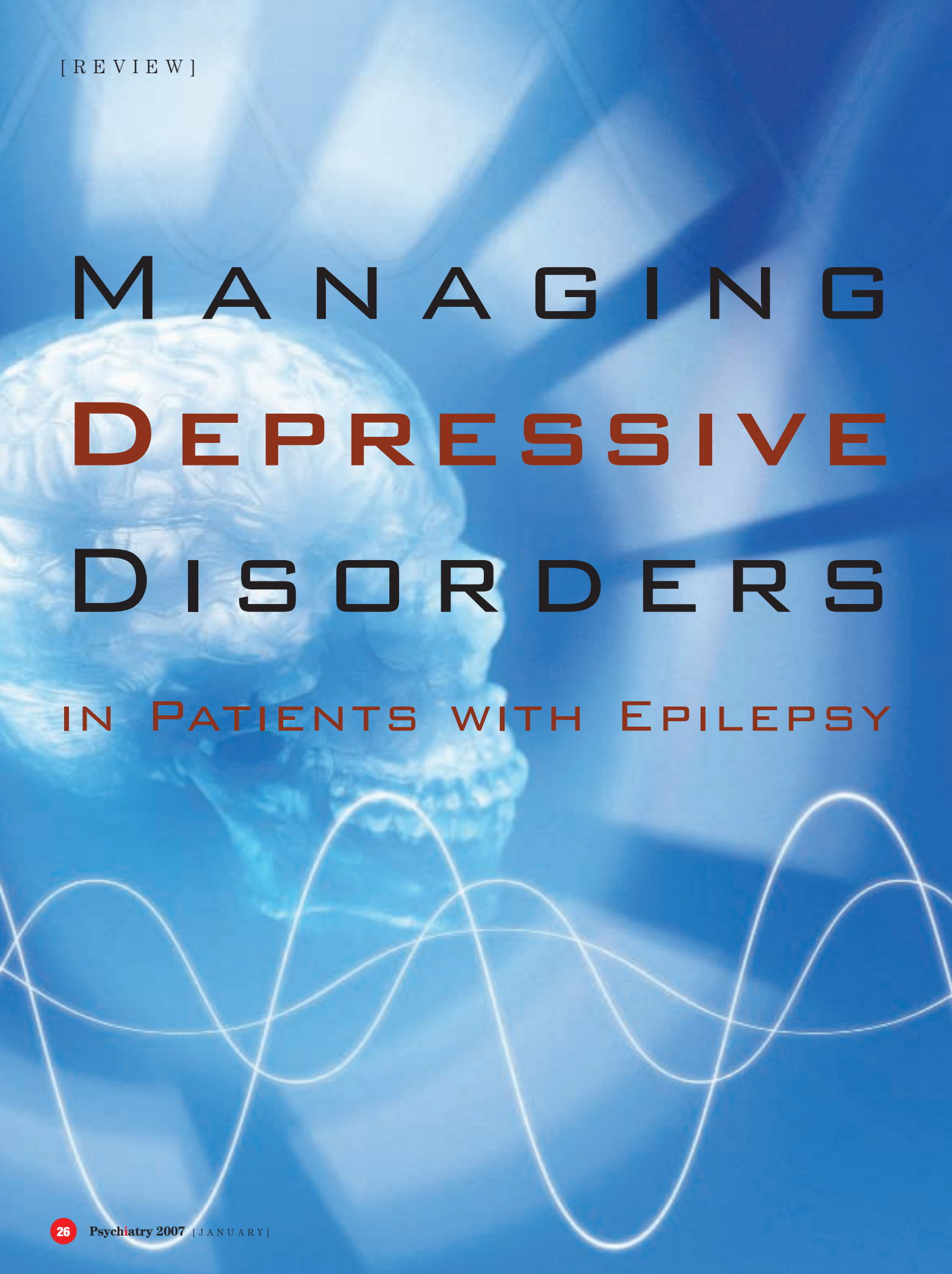

Managing Depressive Disorders in Patients with Epilepsy

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ABSTRACT—Patients with epilepsy are more likely to suffer from psychiatric illnesses, and more specifically depressive disorders (9% to 22%), than the general population. Depression in epilepsy is often described by the temporal correlation to a seizure, with interictal depression being the most commonly described. Furthermore, epileptic patients with depression often report a poorer quality of life on global assessments and are at an increased risk of suicide as compared to the general population, 11.5 percent versus 1.2 percent, respectively. Despite the clinical significance of depression, it often goes unrecognized and hence untreated in this population. Recently, more efforts at screening epilepsy patients for coexisting depression have been undertaken, yielding fair results. However, some epilepsy patients express a certain constellation of symptoms, including an explosive or irritable mood, somatic pains, anxiety and fear, and periods of brief euphoria, which are not captured by common depression screening tools. Fears of antidepressants lowering seizure thresholds coupled with potential pharmacokinetic interactions between antiepileptic and antidepressant medications have strongly contributed to the undertreatment of this population. Finally, the treatment of depressive disorders in epilepsy is understudied and the few existing research studies have yet to display an effective treatment. Depressive disorders in patients with epilepsy pose significant and specific problems with regard to recognition, diagnosis, and treatment that require careful and thorough management.

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DISCLOSURES—Dr. Trivedi acknowledges relationships with the following companies: Research Support—Bristol-Myers Squibb, Cephalon, Corcept Therapeutics, Cyberonics, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Merck, National Institute of Mental Health, National Alliance for Research in Schizophrenia and Depression, Novartis, Pfizer, Pharmacia & Upjohn, Predix Pharmaceuticals, and Solvay; Advisory/Consulting—Abbott Laboratories, Akzo (Organon Pharmaceuticals), Bayer, Bristol-Myers Squibb, Cephalon, Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Johnson & Johnson PRD, Eli Lilly, Meade Johnson, Parke-Davis Pharmaceuticals, Pfizer, Pharmacia & Upjohn, Sepracor, Solvay, and Wyeth-Ayerst Laboratories; and Speaking—Akzo (Organon Pharmaceuticals), Bristol-myers Squibb, Cephalon, Cyberonics, Forest Pharmaceuticals, Janssen Pharmaceutica, Eli Lilly, Pharmacia & Upjohn, Solvay, and Wyeth-Ayerst Laboratories. Dr. Kurian has no relevant conflicts of interest.

KEY WORDS— depression, epilepsy, antidepressants, mood disorders, seizures, medical comorbidity

PREVALENCE OF DEPRESSION IN EPILEPSY

Psychiatric illnesses are commonly found in patients with epilepsy, with major depressive disorder (MDD) being the single most common psychiatric disorder.[1] In patients with comorbid epilepsy and depressive illnesses, the presence of depressive symptoms has been classified temporally with regard to the seizure. Depressive symptoms associated with seizures include 1) periictal depression, for the time immediately before and after a seizure, 2) ictal depression, for symptoms as part of the seizure, 3) postictal depression, usually lasting on average up to 37 hours after a seizure (the least common occurrence), and 4) interictal depression (the most common phenomenon), which generically describes any period between seizures.[2] Prevalence of DSM-IV depressive disorders found in the interictal period in patients with epilepsy varies depending upon the population sampled. For instance, in an outpatient clinic sample of chronic epileptics without regard to type of seizure, a point prevalence of 17.2 percent was identified for MDD.[1] However, among hospitalized inpatients and those with intractable epilepsy, the lifetime prevalence of MDD is much higher, reaching up to 58 percent.[3,4]

ASSOCIATION OF DEPRESSION AND TYPES OF SEIZURES

Among the different types of seizures, temporal lobe epilepsy (TLE), a subtype of complex-partial seizures, has been associated with the highest prevalence of psychiatric comorbidities, including major depression.[5] Furthermore, in a sample of 220 epileptic patients, Piazzini and colleagues found that among TLE patients, those with a left temporal focus had higher depression severity than those with a right focus. A more recent study confirmed these findings and found that patients suffering from a complex partial seizure disorder were much more inclined to have depression morphology compared to those with generalized tonic-clonic seizures.[6]

BURDEN OF DISEASE

Depression is common, often chronic and/or recurrent, and associated with significant morbidity and mortality. MDD is a leading cause of employee disability in the United States that has been estimated to cost employers more than $31 billion per year in lost productivity time.[7] MDD is also commonly associated with other neurological and non-neurological general medical illnesses. The annual prevalence of co-occurring MDD in patients with seizures is 13.6 percent.[8]

The mortality of depression is manifested in suicide, which accounted for over 31,000 cases in the United States in 2003.[9] Suicide risk in epilepsy has been assessed by a number of individuals; in fact, a recent metaanalysis by Pompili and colleagues[10] sorted through 29 cohort studies of epilepsy patients and found that patients suffering with epilepsy were at a higher risk of completing suicide than that of the general population. Jones, et al., quantify this increased risk from a sample of pooled studies to be about 11.5 percent versus 1.1 to 1.2 percent in the general population.[11]

With regard to quality of life measurements, it is well known that one of the strongest indicators of quality of life among epilepsy patients is depression severity.[12,13] In fact, the severity of depression more reliably predicts patient quality of life than seizure frequency.[14,15] This reduction in quality of life in depressed patients with epilepsy leads to more frequent primary care and psychiatric visits and an increased utilization of healthcare in general when compared to nondepressed epilepsy patients.[16]

SCREENING AND RECOGNITION

Unfortunately, despite the high prevalence of depression in epilepsy and the overwhelming effect on the burden of disease, far too often these patients go unrecognized and subsequently untreated. In fact, in a multicenter epidemiologic study of 174 patients, Jones, et al., found that less than half of the patients diagnosed with MDD were being prescribed antidepressant medication.[1] In this same study, the Mini-International Neuropsychiatric Interview (MINI)[17] was assessed as a more logistically feasible application for screening for psychiatric comorbidity than the more traditional Structured Clinical Interview for DSM–IV Axis I Disorders-Research Version (SCID-I).[18] Further, when used in combination with a patient self-report tool, such as the Beck Depression Inventory (BDI)[19] or the Center for Epidemiological Studies Depression Scale (CES-D),[20] both of which offer the ability to effectively rule out depression (a reported negative predictive value of 99.1% for both tests), subsequent use of the MINI was shown to confirm presence of depression.[21]

Given the reports of the underrecognition of depression, the benefit of using screening tools and objective measures in epilepsy patients is clear. However, one potential limitation of this and other traditional screening tools is the lack of an effective screen for specific symptoms of depression in patients with epilepsy (Table 1).[22] Blumer, et al., ascribe the name of "interictal dysphoric disorder" to the following constellation of symptoms: Irritability, depressive moods, anergia, insomnia, atypical pains, anxiety, fears, and euphoric mood. The diagnosis requires that the patient must express at least three of these symptoms.[23] Blumer points to Emil Kraepelin, one of the fathers of psychiatry, as the first to note an episodic symptom subset of irritability, depressed mood, anxiety, headaches, and insomnia specifically amongst epilepsy patients.[23] Kanner describes a similar subset of patients in a prospective study of epileptic patients on antidepressant drug therapy, of which only 28 of 97 met criteria for MDD.[24] The other patients in Kanner's trial exhibited a variant of Blumer's cluster of symptoms that he calls "dysthymic-like disorder of

epilepsy," namely, without insomnia and atypical pains, but with anhedonia (with or without hopelessness), poor frustration tolerance, and mood lability with bouts of crying.[24]

EVIDENCE FOR TREATMENT

To date, few studies have assessed the efficacy of antidepressant medication use in depressed patients with epilepsy (Table 2). In fact, only one randomized, placebo-controlled, double-blind trial has been carried out to assess antidepressant efficacy in depressed epileptics. Robertson and Trimble compared amitriptyline and nomifensine (a dopamine and norepinephrine reuptake inhibitor that was removed from the market) to placebo in a six-week study, and although mean 21-item Hamilton Depression Rating Scale (HAM-D21) scores improved in all groups, no difference existed between treatment groups.[25] However, this study was powered to primarily assess safety; in this respect, no statistically significant differences in seizure frequency were seen among any of the three groups.

Among noncontrolled, open-label pharmacological trials, a fixed dose of citalopram 20mg, added to a stable AED (anti-epileptic drug) regimen, was studied in 45 patients with epilepsy (various seizure disorders) over four months by Specchio and colleagues.[26] In 39 completers, 67 percent were termed as having "marked or moderate improvement" and 18 percent with "remission;" however, neither outcome percentage was clearly identified. The primary endpoint, seizure frequency, was shown to be significantly lower by patient self-report after the addition of citalopram, decreasing from 1.32 seizures/month to 0.82 seizures/month.[26] In looking further at citalopram, Hovorka, et al., assessed flexible dosed citalopram in 43 epilepsy patients diagnosed with MDD, and after eight weeks 65.1 percent (28/43) responded to treatment (i.e., ≥50% reduction in HAM-D21).[27] The mean dose of citalopram in this study was 22.6mg at study end, with no significant

TABLE 1. Diagnostic criteria for major depressive episodes and depressive syndromes in epilepsy

Symptoms	Major Depressive Disorder (MDD)†	Interictal Dysphoric Disorder (IDD)‡	Dysthymic-like Disorder of Epilepsy (DLDE)§
	At least 5 for 2 weeks	At least 3 symptoms	Waxing/Waning course
Depressed Mood	√	√	n/a
Anhedonia	√	n/a	√
Change in weight/appetite (⇑/⇓)	⇑/⇓	n/a	⇑/⇓
Change in sleep(⇑/⇓)	⇑/⇓	⇓	⇑/⇓
Change in psychomotor functioning (⇑/⇓)	⇑/⇓	n/a	n/a
Fatigue, loss of energy	√	√	√
Feelings of worthlessness, guilt	√	n/a	n/a
Diminished concentration, indecisiveness	√	n/a	√
Suicidality	√	n/a	n/a
Irritability/explosive behavior	n/a	√	√
Atypical pains	n/a	√	n/a
Anxiety	n/a	√	√
Fears	n/a	√	n/a
Brief euphoric moods	n/a	√	√

† Diagnostic criteria taken from DSM-IV[51]

‡ Diagnostic criteria taken from Kanner AM.[52]

§ Diagnostic criteria taken from Blumer D, et al.[23]

TABLE 2. Studies assessing antidepressant efficacy in epilepsy

Author	RCT (y/n)	Study Design	Study Population	Treatment Group(s) and Sample Size (*N*)	Depression Outcome Measures	Results
Robertson MM and Trimble MR (1985)	Y	DB, PC	Epilepsy (all types) and depressed (HAM-D_{21} >15)	1. PBO (13) 2. AMI (13) 3. NOM (13) *N*=39	HAM-D_{21} at 6 weeks	No statistically significant difference between any treatment groups
Specchio LM, et al. (2004)	N	Open-label	Epilepsy (all types) and depressed (MADRS ≥20)	1. CIT *N*=45	MADRS, Zung-SDS at 4 months	Remission = 18%†
Hovorka, et al. (2000)	N	Open-label	Epilepsy (all types) and depressed (HAM-D_{21} >15)	1. CIT *N*=43	HAM-D_{21} at 8 weeks	Response§ = 65.1%
Kanner, et al. (2000)	N	Open-label	Epilepsy (95% partial) and depressed (DSM-IV criteria)	1. SERT *N*=100‡	None mentioned	"complete resolution" = 54%
Kühn KU, et al. (2003)	N	*Post-hoc* analysis	TLE (partial and/or generalized) and depressed (HAM-D_{21} >15)	1. MIRT (27) 2. CIT (33) 3. RBX (15) *N*=75	HAM-D_{21} at 4 and 20–30 weeks	Response/Remission¶ MIR = 44.4%/3.7% CIT = 30.3%/6.1% RBX = 53.3%/13.3%

DB = Double blind, PC = Placebo-controlled, PBO = Placebo, AMI = Amitriptyline, NOM = Nomifensine, CIT = Citalopram, SERT = Sertraline

TLE = Temporal Lobe Epilepsy, MIRT = Mirtazapine, RBX = Reboxetine.

† Completer analysis (*N*=39, 6 study dropouts) and remission criterion not specified

§ Response measured as ≥50% reduction in HAM-D_{21}

‡ 28 with major depressive disorder, 69 with depression NOS, 3 with obsessive compulsive disorder

¶ Dropout rates by study end: MIR = 74.1%, CIT = 48.5%, RBX = 40.0%

changes in seizure frequency reported.[27] Similarly, Kanner, et al., looked at sertraline in an open-label study of 100 patients (97 depressed and 3 with obsessive compulsive disorder), and reported 54 percent achieved "complete resolution of depressive symptoms."[28] However, the authors do not report the use of any depressive assessment tool, and it is unknown how they reached this conclusion. Kühn, et al., performed a *post-hoc* analysis that assessed depression outcomes (LOCF) with mirtazapine, citalopram, or reboxetine in patients with temporal lobe epilepsy and at four weeks found meager rates of treatment response (mirtazapine 44.4%, citalopram 30.3%, and reboxetine 53.3%) and remission (mirtazapine 3.7%, citalopram 6.1%, and reboxetine 13.3%).[29] Also of note in this study are the high dropout rates among treatment groups, and the significantly higher dropout rate in the mirtazapine group at study end

(74.1% vs. citalopram 48.5% and reboxetine 40.0%).[29]

Lastly, the benefits of nefazodone were reported in a patient with complex partial seizures and an associated depressive disorder,[30] while in a case series of patients with epilepsy with "interictal dysphoric disorder" and treatment-resistant depression, Blumer advocates the use of "double antidepressant treatment," combining a tricyclic antidepressant with a selective serotonin reuptake inhibitor (SSRI).[31]

The literature is sparse regarding nonpharmaceutical interventions for depression in epilepsy. Davis, et al., conducted a randomized study in which one group of adult epileptics underwent six weeks of cognitive-behavioral therapy (CBT), and compared to a control group the CBT group had significant reductions in depression and dysphoria.[32] However, this study was limited by small sample size, baseline differences between treatment groups, and other methodological flaws. In 1986, Tan and Bruni assessed the effectiveness of group CBT in epileptics, not only as a measure to improve depressive symptoms, but also to decrease seizure frequency.[33] However, aside from the therapists' global ratings, no significant differences were found between groups, although this study was also limited by a small sample size. In a study of six adult women with longstanding complex-partial seizures, Goldstein, et al., applied 12 weeks of individual weekly CBT and found no significant change in depression scores from baseline.[34] In a small sample in Hong Kong, Au, et al., conducted group CBT based on a similar regimen to Tan and Bruni, and although they did not specifically assess depression outcomes, a quality of life inventory was found to be significantly improved in the CBT group versus controls.[35] Lastly, Ramaratnam and colleagues reviewed all published psychological therapies for epilepsy and found that CBT, relaxation therapy, biofeedback, educational interventions, and a combination of behavioral therapy and relaxation

Table 3. CYP isoenzymes and antiepileptic and antidepressant medications†

ENZYME	ANTIDEPRESSANTS	ANTIEPILEPTICS
CYP1A2	SUBSTRATES	INDUCERS
	Tricyclic Antidepressants	Carbamazepine
	Fluvoxamine	Phenytoin
		Phenobarbital
	INHIBITORS	
	Fluvoxamine	
CYP2C9	INHIBITORS	SUBSTRATES
	Fluoxetine	Phenytoin
		Phenobarbital
CYP2D19	SUBSTRATES	SUBSTRATES
	Tricyclic Antidepressants	Phenytoin
	Citalopram	Diazepam
CYP2D6	SUBSTRATES	None
	Tricyclic Antidepressants	
	Fluoxetine	
	Paroxetine	
	Venlafaxine	
	INHIBITORS	
	Fluoxetine	
	Paroxetine	
CYP3A4	SUBSTRATES	SUBSTRATES
	Tricyclic Antidepressants	Diazepam
	Sertraline	Alprazolam
	Nefazodone	Midazolam
		Triazolam
		Carbamazepine
		Tiagabine
		Zonisamide
	INHIBITORS	INDUCERS
	Fluoxetine	Carbamazepine
	Fluvoxamine	Phenytoin
	Nefazodone	Phenobarbital
		Oxcarbazepine
		Topiramate

† Table modified from Spina and Perucca (2002)[44] & Curran and de Pauw (1998)[45]

Drugs in italics are designated as weaker inducers

TAKE-HOME POINTS

1. **Depression in epilepsy is underdiagnosed and undertreated.**

2. **Screen (with either BDI or CES-D) all patients with epilepsy (especially complex-partial) for depression.**
- Depression in epilepsy does not always present classically.
- Watch for additional noncore signs and symptoms (see Table 1).
- A need exists for a screening tool that incorporates additional noncore symptoms.
- Confirm a positive depression screen with a more thorough interview (e.g., MINI).

3. **Treat major depression in patients with epilepsy.**
- Prior to initiating antidepressants, check plasma levels of AEDs.
- Prior to initiating antidepressants, consult with neurologist to monitor baseline seizure frequency.
- When choosing an antidepressant, take precaution to note any potential pharmacokinetic interactions (see Table 2).
- Periodically check plasma drug levels of AEDs and antidepressants – monitoring for toxicity (AED) and decreased efficacy (antidepressant).

4. **Monitor symptoms and treat as you would primary depression.**
- Administer measurement-based scales at each visit (e.g., QIDS-SR16, IDS-SR30, HAM-D).
- Duration of treatment with antidepressant should be based on achieving remission of symptoms.

5. **Depression in epilepsy is understudied, and controlled efficacy trials are warranted.**

have all been attempted in epilepsy patients, but given inconsistent study methods no real conclusions can be drawn regarding any of these treatments.[36]

THE DILEMMA OF TREATING DEPRESSION AND COMORBID EPILEPSY

Proconvulsive potential of antidepressants. As suggested above, depression is underdiagnosed in patients with epilepsy, and this may be due to epilepsy patients presenting with a variant of depressive symptoms. However, depression is also undertreated in patients with epilepsy, partially because of the fear that antidepressant medications may lower the seizure threshold, thereby exacerbating the epilepsy.[37,38] A variety of studies have reviewed the literature regarding antidepressant use and impact on seizure threshold, and Rosenstein, et al., concluded that seizures, even with concomitant antidepressant use, are such rare events that an enormous sample size would be necessary to detect even a small difference in seizure risk from placebo.[39] The mechanism by which certain antidepressants lower seizure thresholds is unclear; however, Montgomery reports that "at lower doses, some antidepressants have anticonvulsant activity, whereas at higher doses, they have proconvulsant activity."[40] Furthermore, seizure risk has been shown not only to vary by antidepressant dose but by drug, with maprotiline and amoxapine reportedly posing the highest risk, while doxepin, trazodone, and fluvoxamine among the older generation of antidepressants pose the smallest risk for antidepressant-induced seizure.[37] Generally, it is believed that the SSRI class of antidepressants has a lower risk for inducing seizures, as shown by an incidence of only 0.1 percent for paroxetine.[41] Most of the studies reporting on risk of seizure induction are done in nonepilepsy patients; however, a small body of literature is present on seizure risk in epilepsy, and the consensus is antidepressants do not significantly increase seizure frequency in epileptics.[25–27, 29, 31, 41–43] After assessing seizure frequency for 12 months at baseline, Kanner, et al., defined worsening of seizure frequency as either "probable" or "definite" in their sample of 100 epileptics taking sertraline. Of these, one was classified as having "definite" worsening and five were "probable."[28] Furthermore, all five of the "probable" worseners responded to an adjustment of their antiepileptic medications, returning back to their baseline seizure frequency. Among the new antidepressant medications, Bupropion appears to pose the highest seizure risk in a dose-dependent manner.

Potential pharmacokinetic interactions. Another major concern regarding antidepressant use in epilepsy surrounds the potential for pharmacokinetic interactions between antiepileptic (AED) and antidepressant medications, via the cytochrome P-450 pathway. The P-450 pathway is composed of various isoenzymes, of which the most well known with regards to drug metabolism are CYP3A4, CYP2D6, CYP2C19, CYP2C9, and CYP1A2. Many antiepileptics and antidepressants are metabolized by these enzymes, and additionally some of these agents serve as substrates, inducers, or inhibitors for these isoenzymes. Table 3 presents the interactions and the potential consequences of these interactions.[44,45] In general, antiepileptic medications, such as phenytoin, carbamazepine, and barbiturates, are potent inducers of the P-450 isoenzymes (namely CYP1A2 and CYP3A4) and thereby can decrease the level of antidepressant medications. On the other hand, SSRIs, such as fluvoxamine, fluoxetine, sertraline, and paroxetine, inhibit, to varying degrees, isoenzyme metabolism and thus can cause elevated antiepileptic blood levels. However, in general most reviews recommend using second-generation SSRIs and SNRIs as first-line treatments for depression in epilepsy, paying specific attention to potential pharmacokinetic interactions, measuring plasma drug

levels, and when possible choosing antidepressants with the least amount of interaction potential.[44,45]

DURATION AND MONITORING OF TREATMENT

No clinical trials in depressed patients with epilepsy have studied duration of treatment as it pertains to remission and time to relapse. As such, no evidence exists as to how long a patient with depression and epilepsy should remain on antidepressant treatment. Of the few antidepressant efficacy studies, most use the HAM-D to measure depressive symptomatology.[46] Further, given the lack of current evidence in treating and measuring depression in epilepsy, it stands to reason to follow the primary depression model. As such, the HAM-D, Montgomery Asberg Depression Rating Scale (MADRS),[47] the Patient Health Questionnaire (PHQ-9),[48] the 30-item Inventory of Depressive Symptomatology—Self-report (IDS-SR30),[49] and the 16-item Quick Inventory of Depressive Symptomatology—Self-report (QIDS-SR16)[50] have all been validated to monitor depressive symptoms on an ongoing basis. However, as mentioned above, depressive symptoms in epileptics may manifest differently from primary depression, and commonly used depression measuring scales need validation in this population. Again, this underscores the need for further controlled clinical trials in this understudied population.

CONCLUSION

In conclusion, patients with epilepsy who also suffer from psychiatric comorbidities represent a substantial population that often goes unrecognized. Furthermore, these individuals are being underdiagnosed and undertreated. Recent measures at screening these individuals have met with some success; however, it appears that the symptom cluster of a subset of these patients does not reflect "classic" major depressive disorder and may require particular attention to the assessment of these specific symptom clusters. Further studies are needed to explore identification of depression in epilepsy and to disseminate current screening tools into practice. A paucity of data currently exists in the realm of evidence-based treatment of depression in patients with epilepsy. Initiating antidepressant treatment in patients with epilepsy must be tempered by cautious monitoring of plasma drug levels of both antiepileptics and antidepressants (when available) and potential pharmacokinetic interactions. The selection of the most appropriate pharmacological and nonpharmacological treatments for depression in epilepsy and the monitoring of outcomes remains largely understudied and an important area for urgent development.

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